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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/673,739	10/20/00	MCCARTHY	T 1377-156P

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EXAMINER	
TUNG, T	
ART UNIT	PAPER NUMBER
1656	11

DATE MAILED:
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/673,739	McCarthy et al.
Examiner	**Art Unit**
Joyce Tung	1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-23 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-23 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1656.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper tames extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.d. 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1-5, 8, 10-12, 14-16 and 20-23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4-7, 12-13, 15-19 of U.S. Patent No. 5,952,176 in view of Chirikjian et al. (5,656,430). Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 1-5, 8, 10-12, 14-16 and 20-23 are drawn to a method of characterizing nucleic acid molecules comprising introducing a modified base which is a substrate of DNA glycosylase into a DNA molecule, excising the modified based by the DNA glycosylase, cleaving the DNA at the abasic

site to generate an upstream DNA fragment that can be extended in the presence of an enzyme and a template nucleic acid and analyzing the resultant fragments. The subject of the instant invention encompasses the method of claims 1, 2, 4-7, 12-13, 15-19 of U.S. Patent No. 5,952,176 because the claims are drawn to a method for rapidly detecting the presence or absence of a particular nucleic acid sequence at a candidate locus involving the steps in instant claims 1-5, 8, 10-12, 14-16 and 20-23 except that in the instant claims an upstream DNA fragment is formed by cleaving the DNA at the abasic site and extended. This technique is taught by Chirikjian et al.. Chirikjian et al. disclose a method for detecting point mutation in nucleic acid sequence in which 5' probe cleaved and binds to a template for DNA polymerase with dNTP (See column 8, lines 47-50).

Specification

3. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Objections

4. Claim 22 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form because claim 22 has not further limitation to claim 1 that claim 1 is also drawn to a method for characterizing nucleic acid molecules.

Claim Rejections - 35 U.S.C. § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-23 are vague and indefinite because of the language "a DNA molecule" in claim 1. It is unclear what is the definition of the language in the specification. Whether or not it is a single stranded or double stranded DNA molecule. It is suggested to clarify uncertainty. In addition, the language "the extendible upstream fragment" and "the resultant fragment" has no antecedent basis from where it is referred.

b. Claim 13 is vague and indefinite because the language "wherein one or more of the nucleotide(s) of step iv) is a dideoxy nucleotide" is not in step iv) of claim 1. It is suggested to amend the language including antecedent basis.

c. Claim 14 is vague and indefinite because the language "wherein one or more of the nucleotide(s) of step iv) is labeled" is not in step iv) of claim 1. It is suggested to amend the language including antecedent basis.

d. Claim 19 is vague and indefinite because the language "the reporter oligonucleotide is partially degenerate". It is unclear how the language is defined in the specification.

Claim Rejections - 35 U.S.C. § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-2 and 8-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCarthy et al. (WO 97/03210) in view of Chirikjian et al. (5,656,430).

McCarthy et al. disclose a method for detecting a nucleic acid sequence at a locus in a target sample nucleic acid. The method involves introducing a modified base which is a substrate for a DNA glycosylase into a DNA molecule, excising the modified base by DNA glycosylase, cleaving phosphate linkages at abasic sites and analyzing the cleaved products of step iii) to

identify the target nucleic acid (See pg. 8, lines 9-22) (as recited in claim 1-2, 4). The locus is amplified using normal DNA precursor nucleotides and at least one modified precursor nucleotide (See pg. 9, lines 5-6) (as recited in claims 10-12, 14, 15,16). The method is used for detecting multiple known mutation in DNA (See pg. 8, lines 23-27) (as recited in claim 21 and 23). The amplification method involves ligase chain reaction and deoxyribonucleotide (See pg. 9, lines 11-18) (as recited in claim 13, and 17). A modified nucleotide can be incorporated into a nucleic acid during amplification (See pg. 9, lines 18-20) (as recited in claim 8). One primer is labeled when an amplification method is used in the invention to allow detection of amplified target or complementary strand alone (See pg. 12, lines 7-10). The detection is done by using appropriate nucleic acid hybridization probe (See pg. 12, lines 22-25) (as recited in claim 20). This suggests that there must be a reporter oligonucleotide for the hybridization probe (as recited in 18). To facilitates detection of the cleaved extended adjacent primer, the extended adjacent primer denatured by denaturating polyacrylamide gel electrophoresis (See pg. 17, lines 9-18) (as recited in claim 9 that the amplified strands are separated for a separate analysis of the respective strands).

McCarthy et al. do not disclose that an upstream fragment formed as claimed is extended with a template and the extendible uptream fragment is incubated with ligase in the presence of a reporter oligonucleotide as recited in claim 18.

Chirikjian et al. disclose a method for detecting point mutation in nucleic acid sequence in which 5' probe cleaved and binds to a template for DNA polymerase with dNTP (See column

8, lines 47-50) and a probe is hybridized to single stranded DNA generating a mismatch in the ssDNA and the new strand is synthesized in vitro with DNA polymerase and ligase (See column 4, lines 7-12).

The teachings of McCarthy et al. and Chirikjian et al. suggest the limitations of claims 1-2 and 8-23. Claims 1-2 and 8-23 are drawn to a method of characterizing nucleic acid molecules involving introducing a modified base which is a substrate for a DNA glycosylase into a DNA molecule, excising the modified base by DNA glycosylase, cleaving phosphate linkages at abasic sites and incubating the extendible upstream fragment in presence of polymerase and a template and analyzing the resultant fragments. The primer or nucleotide is labeled. A ligase is involved. The method involves a reporter oligonucleotide and detection is done by hybridization. The method is also used for analyzing mutation as claimed in claims 21 and 23.

One of ordinary skill in the art at the time of instant invention would have been motivated to apply the teachings of McCarty et al. and Chirikjian et al. to characterize nucleic acid molecules with a reasonable expectation success because the method of McCarthy et al. is used to detect multiple known mutations in DNA which can be achieved rapidly and easily (See pg. 8, lines 23-27) and the method of Chirikjian et al. is efficient and sensitive by using the probe (See column 8, lines 47-50) with labeled nucleotides as the signal (See column 2, lines 48 and column 8, lines 47-49). An ordinary skill in the art would have involved the probe as taught by Chirikjian et al.. Thus, it would have been prima facie obvious to carry out the method as claimed.

9. Claims 3-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCarthy et al. (WO 97/03210) in view of Chirikjian et al. (5,656,430) as applied to claims 1-2 and 8-23 above, and further in view of Dianov et al. (Molecular and Cellular Biology, 1992, Vol. 12(4), pg. 1605-1612).

The teachings of McCarthy et al. and Chirikjian et al. are set forth in section 8 above and the methods of McCarthy et al. and Chirikjian et al. do not involve using 5' AP endonuclease and a 5' deoxyribophosphodiesterase as claimed in claims 3-7 to treat the apurinic and apyridimic sites (See pg. 23, lines 9-15).

Dianov et al. disclose that the extent and location of DNA repair synthesis in a double stranded oligonucleotide containing a single dUMP residue have been determined in which the repair pathway of a dUMP residue in DNA involves uracil- DNA glycosylase and incision of the phosphodiester bond 5' to AP site by an AP endonuclease and baseless sugar-phosphate residue could be excised by a dRpase or a 5'-3'exonuclease to leave a hydroxy group at the 3' terminus (See pg. 1606, fig, 1) (as recited in claims 3-6) and then the polymerase step occur either after of before the excision step. The excision step is catalyzed usually by a DNA deoxyribophosphodiesterase (See pg. 1605, the Abstract) (as recited in claim 7).

The teachings of McCarthy et al., Chirikjian et al. and Dianov et al. suggest the limitations of claims 3-7. Claims 3-7 recite further limitations of claim 1 in which the cleavage is achieved with a 5' apyrimidinic endonuclease, the upstream fragment bears a hydroxyl group at 3' end and 5' deoxyribose moieties are removed by a 5' deoxyribophosphodiesterase.

One of ordinary skill in the art at the time of instant invention would have been motivated to combine the teachings of McCarty et al., Chirikjian et al. and Dianov et al. to characterize nucleic acid molecules with a reasonable expectation success because the method of McCarthy et al. is used to detect multiple known mutations in DNA which can be achieved rapidly and easily (See pg. 8, lines 23-27), the method of Chirikjian et al. is efficient and sensitive by using the probe (See column 8, lines 47-50) with labeled nucleotides as the signal (See column 2, lines 48 and column 8, lines 47-49), and the teachings of Dianov et al. indicate that the enzyme used in excision repair involving AP sites is good candidates to carry out each step in the pathway (See pg. 16, column 1, last paragraph). Thus, it would have been prima facie obvious to carry out the method as claimed with combining the teaching of .McCarty et al., Chirikjian et al. and Dianov et al.

10. Any inquiries concerning this communication or earlier communications from the examiner should be directed to Joyce Tung whose telephone number is (703) 305-7112. The examiner can normally be reached on Monday-Friday from 8:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached at (703) 308-1152.

Any inquiries of a general nature or relating to the status of this application should be directed to the Chemical/Matrix receptionist whose telephone number is (703) 308-0196.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Art Unit 1656 via the PTO Fax Center located in Crystal

Mall 1 using (703) 305-3014 or 308-4242. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Joyce Tung

June 30, 2001